REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-6, 9, 11, 20-21, 28-33, 37-55, 59-63 and 68-70 are pending. Non-elected claims 7-8 and 64-67 were withdrawn from consideration by the Examiner. Applicants cancel the nonelected claims without prejudice to future prosecution of that subject matter. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry.

Claims 2-3, 5-6, 9 and 33 were withdrawn from consideration by the Examiner as allegedly being drawn to nonelected inventions or species. It was further alleged that there is no allowable generic or linking claim. Applicants request rejoinder of claims 2-3, 5-6, 9 and 33. Claim 9 further defines the amino acid sequence of the polypeptide having the amino acid sequence shown in SEQ ID NO: 1 of the C-terminal domain of ApoE-CTD or an amino acid sequence of a part thereof. The Action mailed October 10, 2007 required election of an antibody species including sequences of the three heavy chain CDRs and the three light chain CDRs, but it did not require the election of a polypeptide species. Thus, rejoinder of claim 9 which recites the amino acid sequence of the polypeptide is requested.

Claim 33 recites an antibody or antibody fragment which comprises the heavy chain sequence shown in SEQ ID NO: 40 and the light chain sequence shown in SEQ ID NO: 518 and/or 519 or the light chain sequence shown in SEQ ID NO: 520 and/or 521. SEQ ID NO: 40 is a heavy chain variable region sequence that comprises the heavy chain CDR sequences shown in SEQ ID NOS: 24 to 26 (see Table 8 at page 94 of the specification and Annex 1). SEQ ID NOS: 518 and 520 are light chain variable region sequences that each comprise the light chain CDR sequences shown in SEQ ID NOS: 33 to 35 (see Tables 8 and 21, Example 33 at page 80 of the specification, and Annex 1). SEQ ID NOS: 519 and 521 are light chain constant region sequences (see Table 21 at page 123 of the specification). Therefore, claim 33 is directed to the elected antibody species and rejoinder of this claim is requested.

Claim 1 is amended to recite that it:

(i) binds to a polypeptide having the amino acid sequence shown in SEQ ID NO: 1 of the C-terminal domain of Apolipoprotein E (ApoE-CTD) or the amino acid sequence of a part thereof;

(ii) binds to human plaques; and

(iii) comprises:

(a) a heavy chain CDR3 region comprising the sequence shown in SEQ ID NO: 26, or an affinity matured variant thereof;

(b) a heavy chain CDR2 region comprising the sequence shown in SEQ ID NO: 25, or an affinity matured variant thereof;

(c) a heavy chain CDR1 region comprising the sequence shown in SEQ ID NO: 24, or an affinity matured variant thereof;

(d) a light chain CDR3 region comprising the sequence shown in SEQ ID NO: 35, or an affinity matured variant thereof;

(e) a light chain CDR2 region comprising the sequence shown in SEQ ID NO: 34, or an affinity matured variant thereof; and

(f) a light chain CDR1 region comprising the sequence shown in SEQ ID NO: 33, or an affinity matured variant thereof.

Claim 1 is a generic claim that links the species of claims 2-3 and 5-6. Claim 1 recites an antibody having the CDR sequences shown in SEQ ID NOS: 24 to 26 and 33 to 35 and variants thereof. Several variants of these sequences are disclosed in Applicants' specification which also provides a clear description of further variants and how the skilled artisan may make and/or use them. The CDR sequences set out in claims 2-3 and 5-6 are all affinity matured variants of the CDR3 sequence shown in SEQ ID NO: 26. Therefore, rejoinder of claims 2-3 and 5-6 is requested because claim 1 is a generic linking claim.

Further, under the Commissioner's Notice of March 26, 1996 (1184 OG 86) implementing the Federal Circuit's decisions of *In re Ochiai*, 37 USPQ2d 1127 (1995) and *In re Brouwer*, 37 USPQ2d 1663 (1996), Applicants request rejoinder of the non-elected method claims upon an indication that an elected product claim is allowable.

Specification/Claim Objections

The brief description of the drawings is amended to refer to the different parts of Figs. 1-2 and 9. Withdrawal of the objection to the specification is requested.

The Examiner objected to claims 4 and 37-41 as being of allegedly improper dependent form. Claim 1 is amended as described above. In accordance thereto, the heavy chain CDR3 region and the light chain CDR1, CDR2 and CDR3 regions defined in claims 4 and 37-39 are affinity matured variants of the heavy chain CDR3 region and the light chain CDR1, CDR2 and CDR3 regions having the sequences set out in claim 1. Annex 1 shows the alignments of each of the CDR sequences recited in claim 1 with the affinity matured variant CDR sequences recited in the dependent claims.

The heavy chain sequence defined in claim 40 and the light chain sequences defined in claim 41 are specific heavy chain variable region and light chain variable region sequences that comprise the heavy chain and the light chain CDR1, CDR2 and CDR3 sequences, or affinity matured variants of those sequences, as set out in claim 1. Annex 1 illustrates where the CDR sequences recited in claim 1, or affinity matured variants thereof, occur within the heavy chain and light chain variable region sequences recited in claims 40 and 41.

Therefore, claims 4 and 37-41 are in proper dependent form as they further limit the subject matter of a previous claim. Withdrawal of the claim objections is requested.

35 U.S.C. 112 – Definiteness

Claims 54-55 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

Claim 1 as amended specifies a human, humanised or chimeric antibody. Claim 54 requires a humanised antibody of claim 1. Claim 55 requires a chimeric antibody of claim 1. Claims 54 and 55 are therefore clear and definite.

Applicants request withdrawal of the Section 112, second paragraph, rejection.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 1, 4, 11, 20-21, 28-32, 37-41, 51-55, 59-60 and 68 were rejected because "the specification, while being enabling for a human antibody or antibody fragment which binds to the C-terminal domain of ApoE and comprises either a heavy chain and a light chain or three CDRs of the heavy chain and three CDRs of the light chain," allegedly "does not reasonably provide enablement for an antibody comprising fewer than six CDRs. It was further alleged that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Applicant traverses.

Claim 1 is amended to recite: "An isolated human, humanised or chimeric antibody or antibody fragment, which antibody or fragment:

(i) binds to a polypeptide having the amino acid sequence shown in SEQ ID NO: 1 of the C-terminal domain of Apolipoprotein E (ApoE-CTD) or the amino acid sequence of a part thereof;

(ii) binds to human plaques; and

(iii) comprises:

  (a) a heavy chain CDR3 region comprising the sequence shown in SEQ ID NO: 26, or an affinity matured variant thereof;

  (b) a heavy chain CDR2 region comprising the sequence shown in SEQ ID NO: 25, or an affinity matured variant thereof;

  (c) a heavy chain CDR1 region comprising the sequence shown in SEQ ID NO: 24, or an affinity matured variant thereof;

(d) a light chain CDR3 region comprising the sequence shown in SEQ ID NO: 35, or an affinity matured variant thereof;

(e) a light chain CDR2 region comprising the sequence shown in SEQ ID NO: 34, or an affinity matured variant thereof; and

(f) a light chain CDR1 region comprising the sequence shown in SEQ ID NO: 33, or an affinity matured variant thereof."

Claim 1 as amended thus requires that the antibody comprises six CDRs.

The present specification discloses several antibodies that bind to the C-terminal domain of ApoE. Applicants identified an antibody having the heavy chain CDR1, CDR2 and CDR3 sequences shown in SEQ ID NOS: 24, 25 and 26, respectively and light chain CDR1, CDR2 and CDR3 sequences shown in SEQ ID NOS: 33, 34 and 35, respectively, that binds to the C-terminal domain of ApoE. This antibody is referred to in their specification as "807A-M0028-B02" (see Table 8 at page 94, line 2). Applicants also produced affinity matured variants of this antibody, which variants retain the ability to bind to the C-terminal domain of ApoE. The CDR sequences of these affinity matured variants are described in Table 38 at page 144 of their specification and the sequences of selected variants are shown in Tables 43 and 44 at pages 149-150 of their specification.

Applicants' specification also discloses methods that may be used to obtain affinity matured variants (see page 28, line 2, to page 30, line 20) and describes how the affinity matured variants of an antibody having the heavy chain CDR sequences shown in SEQ ID NOS: 24 to 26 and the light chain CDRs shown in SEQ ID NOS: 33 to 35 were obtained (see Examples 38 and 39 at pages 82-89).

The present specification thus provides sufficient disclosure that would enable the skilled artisan to make and/or use not only an antibody having the CDR sequences of SEQ ID NOS: 24 to 26 and the light chain CDR sequences of SEQ ID NOS: 33 to 35, but also to make and/or use affinity matured variants of these sequences that bind to the C-terminal domain of ApoE and to human plaques.

Therefore, Applicants' specification enables a person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use their invention commensurate in scope with the present claims.

Claim 60 was rejected as allegedly "failing to comply with the enablement requirement." It was further alleged that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants traverse.

Claim 60 recites a method of treating a subject suffering from an amyloid disorder comprising administering to said subject a therapeutically effective amount of an antibody or antibody fragment that binds to the C-terminal domain of ApoE.

The Examiner acknowledges that the specification discloses a mouse model of Alzheimer's disease in which the presence of ApoE in brain plaques can be detected with an antibody that binds to the C-terminal domain of ApoE, but she objects that Applicants' specification does not disclose whether the binding of the antibody results in the removal of existing plaques or the inhibition of formation of new plaques.

Huang *et al* teach that C-terminal truncated forms of ApoE are present to a greater extent in brains of subjects affected by Alzheimer's disease than in normal brains. The present specification demonstrates that the C-terminal truncated forms of ApoE are present in plaques. Therefore, the antibodies of the claimed invention bind to ApoE in plaques. The bound antibodies would facilitate the destruction of the plaques as the plaques become coated with antibody, which will trigger direct destruction of the plaques by immune mechanisms such as complement-dependent cytotoxicity (CDC) or antibody-dependent cellular cytotoxicity (ADCC). For example, the antibody-coated plaques can be removed by phagocytosis, such as by internalization by microglia (see page 49, line 30, to page 50, line 19, of the specification).

Applicants' specification demonstrates that the antibodies that bind to ApoE-CTD were able to stimulate phagocytic uptake of CTD-bearing beads by human macrophage/microglia-like cells in a concentration-dependent fashion (see Example 32 at pages 78-79). Therefore, the present specification provides evidence that antibody binding to

ApoE-CTD in amyloid plaques would facilitate removal of the plaques. This working example is not contradicted by any evidence or reasoning provided in the Action.

Therefore, Applicants' specification discloses their invention in such a way as to enable one of skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the claimed invention.

Withdrawal of the enablement rejections is requested because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

35 U.S.C. 101 –Utility

Claims 1, 4, 11, 20-21, 28-32, 37-41, 51-55 and 59 were rejected as allegedly directed to nonstatutory subject matter. Adoption of the Examiner's suggestion to insert --isolated-- moots this objection. Withdrawal of the rejection is requested.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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Annex 1: Antibody Heavy and Light Chain Sequences

Heavy Chain CDR3 sequences

SEQ ID NO: 26 **Ser Val Leu Leu Asp Tyr**
SEQ ID NO: 512 Xaa_1 Xaa_2 **Leu** Xaa_3 **Asp** Xaa_4
SEQ ID NO: 516 Gly Xaa_2 **Leu** Xaa_3 **Asp** Xaa_4
SEQ ID NO: 20 **Ser** Xaa_5 Xaa_5 **Leu Asp Tyr**
SEQ ID NO: 23 **Ser** Leu Asp **Leu Asp Tyr**
SEQ ID NO: 207 Gly Val Leu Asp His **Tyr**
SEQ ID NO: 208 Gly Ile **Leu** His **Asp Tyr**
SEQ ID NO: 209 Gly **Val Leu Leu Asp** Lys
SEQ ID NO: 210 Gly **Val Leu** Phe **Asp** Asn

Xaa_1 = **Ser** or Gly
Xaa_2 = **Val** or Ile
Xaa_3 = **Leu**, His or Phe
Xaa_4 = **Tyr**, Asn or Lys
Xaa_5 = any amino acid

Heavy Chain CDR2 sequence

SEQ ID NO: 25 **Ser Ile Trp Pro Ser Gly Gly Gln Thr Trp Tyr Ala Asp Ser Val Lys**

Heavy Chain CDR1 sequence

SEQ ID NO: 24 **Met Tyr Met Met Asp**

Light Chain CDR3 sequences

SEQ ID NO: 35 **Leu Gln Tyr Asp Ser Phe Pro Tyr Thr**
SEQ ID NO: 269 Gln **Gln Tyr** Lys Thr Tyr **Pro** Phe **Thr**
SEQ ID NO: 275 **Leu Gln** Pro Glu Thr Tyr **Pro** Trp **Thr**
SEQ ID NO: 268 Gln **Gln Tyr Asp** Ala **Phe Pro** Phe **Thr**

Light Chain CDR2 sequences

SEQ ID NO: 34 **Glu Ala Ser Ile Leu Gln Ser**
SEQ ID NO: 247 Gly **Ala Ser** Thr Val **Gln Ser**
SEQ ID NO: 252 His **Ala Ser** Thr **Leu Gln Ser**

Light Chain CDR1 sequences

SEQ ID NO: 33 **Arg Thr Ser Gln Asp Ile Arg Asn His Leu Gly**
SEQ ID NO: 219 Gln Ala **Ser Gln Asp Ile** Ser **Asn** Tyr **Leu** Asn
SEQ ID NO: 226 **Arg** Ala **Ser** Arg Gly **Ile Arg Asn** Asn **Leu** Ala
SEQ ID NO: 218 **Arg Thr Ser Gln Asp Ile** Gly **Asn His Leu** Ala

Heavy Chain Variable Region Sequences

SEQ ID NO: 40 (SEQ ID NOS: 24, 25 and 26 underlined)

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Met Tyr
            20                  25                  30

Met Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Trp Pro Ser Gly Gly Gln Thr Trp Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ser Val Leu Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser
        115
```

SEQ ID NO: 317 (SEQ ID NOS: 24, 25 and 208 underlined)

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Met Tyr
            20                  25                  30

Met Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Trp Pro Ser Gly Gly Gln Thr Trp Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Ile Leu His Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser
        115
```

SEQ ID NO: 318 (SEQ ID NOS: 24, 25 and 209 underlined)

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser **Met Tyr**
20 25 30

Met Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser **Ser Ile Trp Pro Ser Gly Gly Gln Thr Trp Tyr Ala Asp Ser Val**
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg **Gly Val Leu Leu Asp Lys** Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

SEQ ID NO: 319 (SEQ ID NOS: 24, 25 and 210 underlined)

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser **Met Tyr**
20 25 30

Met Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser **Ser Ile Trp Pro Ser Gly Gly Gln Thr Trp Tyr Ala Asp Ser Val**
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg **Gly Val Leu Phe Asp Asn** Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

Light Chain Variable Region Sequences

SEQ ID NO: 518 (SEQ ID NOS: 33, 34 and 35 underlined)

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Arg Thr Ser Gln Asp Ile Arg Asn His
            20                  25                  30

Leu Gly Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Gln Arg Leu Ile
        35                  40                  45

Arg Glu Ala Ser Ile Leu Gln Ser Gly Val Pro Ser Thr Phe Tyr Gly
    50                  55                  60

Ser Gly Tyr Gly Arg Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Asp Ser Phe Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
105                 110                 115
```

SEQ ID NO: 520 (SEQ ID NOS: 33, 34 and 35 underlined)

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Arg Thr Ser Gln Asp Ile Arg Asn His
            20                  25                  30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45

Tyr Glu Ala Ser Ile Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Asp Ser Phe Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

SEQ ID NO: 43 (SEQ ID NOS: 33, 34 and 35 underlined)

Gln Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1 5 10 15

Gly Asp Arg Val Thr Ile Thr Cys **Arg Thr Ser Gln Asp Ile Arg Asn**
20 25 30

His Leu Gly Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Gln Arg Leu
35 40 45

Ile Arg **Glu Ala Ser Ile Leu Gln Ser** Gly Val Pro Ser Thr Phe Tyr
50 55 60

Gly Ser Gly Tyr Gly Arg Glu Phe Thr Leu Thr Ile Ser Ser **Leu Gln**
65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Asp Ser Phe Pro
85 90 95

Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

SEQ ID NO: 295 (SEQ ID NOS: 219, 247 and 269 underlined)

Gln Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1 5 10 15

Gly Asp Arg Val Thr Ile Thr Cys **Gln Ala Ser Gln Asp Ile Ser Asn**
20 25 30

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Gln Arg Leu
35 40 45

Ile Tyr **Gly Ala Ser Thr Val Gln Ser** Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Asp Asp Phe Ala Thr Tyr Tyr Cys **Gln Gln Tyr Lys Thr Tyr Pro**
85 90 95

Phe Thr Phe Gly Gln Gly Thr Arg Leu Asp Ile Lys
100 105

SEQ ID NO: 294 (SEQ ID NOS: 218, 34 and 268 underlined)

```
Gln Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1               5                  10                  15

Gly Asp Arg Val Thr Ile Thr Cys Arg Thr Ser Gln Asp Ile Gly Asn
            20                  25                  30

His Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Gln Arg Leu
        35                  40                  45

Ile Arg Glu Ala Ser Ile Leu Gln Ser Gly Val Pro Ser Thr Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65                  70                  75                  80

Pro Glu Asp Phe Ala Ser Tyr Tyr Cys Gln Gln Tyr Asp Ala Phe Pro
                85                  90                  95

Phe Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

SEQ ID NO: 302 (SEQ ID NOS: 226, 252 and 275 underlined)

```
Gln Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1               5                  10                  15

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Thr Asn
            20                  25                  30

Tyr Leu Ala Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Arg Leu
        35                  40                  45

Ile Tyr His Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65                  70                  75                  80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Pro Glu Thr Tyr Pro
                85                  90                  95

Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

Light Chain Constant Region Sequences

SEQ ID NO: 519

```
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1               5                  10                  15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20                  25                  30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35                  40                  45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    50                  55                  60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65                  70                  75                  80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                85                  90                  95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105
```

SEQ ID NO: 521

```
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1               5                  10                  15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20                  25                  30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35                  40                  45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    50                  55                  60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65                  70                  75                  80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                85                  90                  95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105
```